Journal Pre-proof

Multiple Sleep Latency Test and Polysomnography in Patients with Central Disorders of Hypersomnolence

Anelia Dietmann, Camilla Gallino, Elena Wenz, Johannes Mathis, Claudio L.A. Bassetti

PII: S1389-9457(20)30587-6

DOI: https://doi.org/10.1016/j.sleep.2020.12.037

Reference: SLEEP 4704

To appear in: *Sleep Medicine*

Received Date: 20 October 2020

Revised Date: 25 December 2020

Accepted Date: 29 December 2020

Please cite this article as: Dietmann A, Gallino C, Wenz E, Mathis J, Bassetti CLA, Multiple Sleep Latency Test and Polysomnography in Patients with Central Disorders of Hypersomnolence, *Sleep Medicine*, https://doi.org/10.1016/j.sleep.2020.12.037.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier B.V.

source: https://doi.org/10.48350/150953 | downloaded: 4.5.2023

Journal Pre-proof

Multiple Sleep Latency Test and Polysomnography in Patients with Central Disorders of Hypersomnolence

Anelia Dietmann[1], Camilla Gallino[1], Elena Wenz[1,2], Johannes Mathis[1,3], Claudio L.A. Bassetti[1,4]

[1]Department of Neurology, Sleep-Wake-Epilepsy-Center, Inselspital, University Hospital and University of Bern, Bern, Switzerland

[2]Graduate School for Health Sciences, University of Bern, Switzerland

[3]Sleep Medicine Practice, Center of Neurology, Bern, Switzerland

[4]Neurology Department, Sechenov First Moscow State Medical University, Moscow, Russia

Corresponding Author

Dr. Anelia Dietmann, PhD

Department of Neurology, University Hospital Inselspital Bern and University of Bern

Freiburgstrasse 18

3010 Bern, Switzerland

Tel: +41 31 66 4 06 13

Fax: +41 632 94 48

mail: anelia.dietmann@insel.ch

Word count: 2475

References: 22

Tables: 3

Figures: 1

Journal Pre-proof

Journal Pre-proof

Abstract

A multiple sleep latency test (MSLT) with occurrence of sleep onset REM periods (SOREMP) is considered one of the central diagnostic criteria for narcolepsy according to the International Classification of Sleep Disorders, but its sensitivity and specificity have been questioned. This study aims to describe MSLT and polysomnography (PSG) findings, including frequency and distribution of SOREMP during the day, in a large cohort of patients with central disorders of hypersomnolence (CDH).

We retrospectively analyzed electrophysiological data from MSLT and PSG in 370 consecutive patients with narcolepsy type 1 (NT1, n = 97), type 2 (NT2, n = 31), idiopathic hypersomnia (IH, n = 48), nonorganic hypersomnia (NOH, n = 116) and insufficient sleep syndrome (ISS, n = 78).

NT1 and NT2 patients had a significantly shorter mean Sleep Latency (mSL) and REM-Latency (REML) in MSLT and PSG. SOREMP occurred more frequently in narcoleptic vs. non-narcoleptic patients in MSLT and PSG. Occurrence of 3 or more SOREMP in MSLT and a SOREMP in PSG had a very high specificity and positive predictive value (98%/96% and 100% respectively), however relatively low sensitivity (65% and 45% respectively).

NT1 more than NT2 patients have shorter mSL and more frequent SOREMP in MSLT and shorter SL as well as REML during nocturnal PSG. Increasing numbers of SOREMP in MSLT and especially SOREMP during PSG increase specificity on the expense of sensitivity in diagnosing narcolepsy. Therefore, frequency of SOREMP in MSLT naps and PSG can help to discriminate but not clearly separate narcoleptic from non-narcoleptic patients.

Keywords: Central disorders of hypersomnolence, Narcolepsy, Idiopathic hypersomnia, nonorganic hypersomnia, Multiple Sleep Latency Test, Polysomnography

Journal Pre-proof

Journal Pre-proof

Introduction

Excessive daytime sleepiness (EDS) was reported by up to 28% of the general adult US population in a study by Ohayon et al., but the prevalence depends on the exact definition [1]. According to the International Classification of Sleep Disorders (ICSD-3), EDS for at least 3 months is the main feature of central disorders of hypersomnolence (CDH) [2]. EDS is often underrated by patients, leading to underdiagnosis and undertreatment of sleep-wake disorders [3]. Subjective sleepiness is usually measured by the Epworth Sleepiness Scale (ESS)[4], a simple self-administered questionnaire, whereas the multiple sleep latency test (MSLT) is the most often used objective method [5].

The occurrence of ≥ 2 sleep onset REM periods (SOREMP) during the MSLT including the nocturnal Polysomnography (PSG) is an essential criterion for the diagnosis of narcolepsy type 1 (NT1) as well as narcolepsy type 2 (NT2) according to the ICSD-3 criteria [2]. However, the sensitivity and specificity of SOREMP for narcolepsy have been questioned over the last few years, since several studies demonstrated the presence of ≥ 2 SOREMP in a series of other diseases. In a cohort of healthy adults multiple SOREMP were detected in 13% of males and 6% of females; some of these healthy subjects even had a mSL of ≤ 8 min formally fulfilling electrophysiological criteria for NT1 or NT2 [6]. Seneviratne et al. found that up to 14% of patients with sleep-disordered breathing (SDB) had 2 or more SOREMP in the MSLT with a mean sleep latency (mSL) of 4.5 min in a clinically sleepy patient group [7]. Marti et al. found that 15% of patients with behaviorally induced insufficient sleep syndrome (ISS) had an MSLT suggestive of narcolepsy (mSL ≤ 8 min and at least two SOREMP) [8]. In line with these findings Drakatos et al. found 1 SOREMP in the MSLT of IH (1%), ISS (7.14%) and periodic limb movement disorder (4.7%) patients [9]. However, in the same study sleep stage sequence analysis discovered, that SOREMP arising from stage N1 has a high sensitivity for NT1 diagnosis, since IH, ISS, PLMD and NT2 patients had mostly SOREMP arising from stage N2 [9]. The same study demonstrated that only narcoleptic patients present with SOREMP in the fourth (afternoon) nap of MSLT [9]. Occurrence of SOREMP during nocturnal PSG has been found highly specific for NT1 [10].

The aim of our present study was to test the current hypothesis of a specific temporal distribution pattern of SOREMP in MSLT and PSG in a large cohort of CDH patients comparing five diagnostic groups, including nonorganic hypersomnia patients.

Patients and Methods

The current study was approved by the local ethical committee (Kantonale Ethikkommission Bern, 2016-00409). For this study, we used data from a clinical registry from the Sleep-Wake-Epilepsy Center of the Department of Neurology at the Inselspital in Bern, initiated in 1997. Clinical and electrophysiological data from each consecutive patient consultation, that included electrophysiological examinations at the Sleep-Wake-Epilepsy-Center, Department of Neurology, University Hospital Bern, Inselspital, were entered into the database manually.

For the present study, all data sets from 2001 until 2016 were extracted from the original clinical registry and transferred to a Research Electronic Data Capture (REDCap®) database containing only coded clinical and electrophysiological data. Study data were collected and managed using REDCap® electronic data capture tools hosted at the department of Neurology, University Hospital and University of Bern, Inselspital, Bern, Switzerland[11,12]. REDCap® is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Each original data set contained a final diagnosis (according to the third or second edition or earlier versions of the international classification of sleep disorders from the American Academy of Sleep Medicine (AASM)). After data transfer all records were reviewed and confirmed manually by two sleep specialists [2]. In cases of a documented change in diagnosis during a follow-up consultation (e.g., initially NT1 after electrophysiological workup, however changed to ISS after hypocretin measurement and due to clinical judgment during follow-up consultations), the final diagnosis was used for the analysis, irrespectively of the initial interpretation of diagnostic workup. The term nonorganic hypersomnia is used as an alternative name of hypersomnia associated with a psychiatric disorder in ICSD 3 and is also described in ICD-10 under the Code F51.1. Excessive daytime sleep or sleep attacks not accounted for by inadequate sleep and/or prolonged transition to the fully aroused state upon awakening (sleep drunkenness) are criteria for NOH under the ICD-10[13]. A description of NOH classification in our cohort has been published elsewhere[14].

Exclusion criteria included incomplete clinical information, incomplete sleep-wake test datasets, as well as the presence of other sleep comorbidities with a potential effect on sleep architecture or unclear CDH diagnosis.

We analyzed electrophysiological data from PSG and MSLT, as well as HLA DQB1*0602 status and CSF hypocretin-1 concentration data, if available, from five selected diagnostic groups with CDH, namely NT1, NT2, IH, non-organic hypersomnia (NOH) and ISS. The sleep latency (SL) and REM-latency

Journal Pre-proof

(REML) from PSG and the individual mean sleep latency (mSL) and individual mean REM-latency (mREML) from MSLT were compared between groups by comparing their median values. Proportions of patients with SOREMP occurring on PSG or MSLT naps were compared between groups. However, for SOREMP analysis only descriptive statistics were used since groups were – as expected – very heterogeneous. If no REM appeared in a single MSLT or PSG trial, subjects were not considered for REM-Latency or SOREMP analysis. CSF hypocretin-1 levels <20 pg/mL were referred to as undetectable hypocretin-1, levels between 20 and 110 pg/mL were considered as low, whereas levels >110 were considered as normal.

Statistical analyses and graphs were performed by Stata/MP 16.0. Data were described by medians (interquartile range (IQR). To compare continuous measures among the five groups, we used the Kruskal Wallis test. We used χ^2 test to compare categorical variables. Significance was accepted at $p < 0.05$.

Results

Patients

We analyzed clinical and electrophysiological data of 370 consecutive patients with clear-cut CDH diagnoses from our center over 15 years (2001-2016). Patients not fulfilling diagnostic criteria or largely incomplete datasets were not included in the analysis. As summarized in table 1, 97 (26%) patients were diagnosed with NT1, 31 (8%) with NT2, 48 (13%) with IH, 116 (31%) with NOH, and 78 (21%) with ISS. HLA DQB1*06:02 status and hypocretin measurements when available are given in table 1.

Electrophysiological studies

Overall, 349 patients underwent PSG and 313 MSLT. Overall, 292 (79%) patients underwent both PSG and MSLT, while 56 (15%) had only PSG. 77% patients completed 5 MSLT trials, 21% 4 trials and 2% less than 4 trials.

Multiple Sleep Latency Test (MSLT)

As shown in figure 1, the median mSL overall patients was 5.1 (Interquartile Range IQR 4.9 min, n=313), shortest for NT1 with 2.7 (IQR 2.4, n=84) min, NT2 with 4.0 (IQR 3.8, n=31) min, IH with 5.2 (IQR 4.3, n=48) min, NOH with 7.4 (IQR 4.5, n=97) min and ISS with 5.3 (IQR 6, n=53) min. REM sleep in any MSLT round occurred in overall 133 (43%) patients, in 77 (92%) NT1, 29 (94%) NT2, 6 (12.5%) IH, 13 (13%) NOH and 8 (15%) ISS patients. The median mREML overall patients was 6.7 (IQR 5.9)

Journal Pre-proof

min, shortest for NT1 with 6.0 (IQR 5.4) min, NT2 with 7.1 (IQR 3.1) min, IH with 10.5 (IQR 2.5) min, NOH with 9.5 (IQR 7.8) min and ISS with 9.8 (IQR 5.8) min.

As shown in table 2, SOREMP (as defined by REML <15min after sleep onset) occurred during any MSLT nap in 92% of NT1 patients, in 94% of NT2 patients, in 13% of IH patients, in 13% of NOH patients and in 15% of ISS patients ($p < 0.0001$, table 2). Up to three or more SOREMP in the course of 5 MSLT naps occurred in 75% of NT1 patients and only 39% of NT2, 2% of NOH or ISS patients and none of the IH patients (table 2).

Polysomnography (PSG)

As shown in figure 1 the median SL overall patients was 6 (IQR 9.5, n=349) min, shortest for NT1 with 3.1 (IQR 4, n= 93,) min compared to NT2 with 7.0 (IQR 9.5, n= 29) min, IH with 5.0 (IQR 5, n= 45) min, NOH with 11.0 (IQR 21, n=109) min and ISS with 5.5 (IQR 8, n=73) min. The median PSG REML was overall 91 (IQR 85) min, shortest for NT1 with 11.8 (IQR 87) min, NT2 with 70.5 (IQR 42.5) min, IH with 93.0 (IQR 75.5) min, NOH with 128.8 (IQR 96.25) min and ISS with 95.0 (IQR 68.5) min.

SOREMP during PSG were found overall patients in 16% (n = 55), in 53% (n = 49) of NT1 patients, 21% (n = 6) of NT2 patients and no SOREMP was registered in IH, NOH or ISS patients ($p<0.0001$), as described in table 2.

Sensitivity, specificity and positive predictive value of SOREMP

As expected by definition, narcoleptic patients had significantly more MSLT and PSG SOREMP compared to non-narcoleptic patients ($p < 0.001$, table 3). Using ICSD3 criteria[2] of two or more SOREMP in either two of the MSLT naps or one SOREMP in PSG and at least one SOREMP in MSLT naps had a high sensitivity of 90% and specificity of 95% with a positive predictive value of 91% discriminating narcoleptic vs. non-narcoleptic patients. Testing criteria of SOREMP in 3 or more MSLT naps had a sensitivity of 65%, specificity of 98% and positive predictive value (PPV) of 96% in discriminating narcoleptic vs. non-narcoleptic patients. SOREMP in PSG had a lower sensitivity of 45%, higher specificity of 100% and PPV of 100%. Combined, 3 or more SOREMP in MSLT and SOREMP in PSG had an even lower sensitivity of 38%, specificity and PPV of 100%.

Discussion

The present study investigated diagnostic parameters of MSLT and PSG in a large cohort of 370 CDH patients, comparing five different diagnostic groups.

The main finding of our study is, as expected, significantly shorter mSL and REML in MSLT and PSG in NT1 compared to non-narcoleptic patients. Furthermore, distinguishing features for narcolepsy vs non-narcoleptic sleepy patients were up to three or more SOREMP in the course of the 5 MSLT naps (75% NT1 vs. 2% NOH, 2% ISS, 0% IH) and SOREMP in the PSG (53% NT1, 0% in IH, NOH, ISS). Applying AASM ICSD3 criteria[2] of 2 or more SOREMP in MSLT (including PSG) had a high sensitivity (90%), specificity (95%) and positive predictive value (91%) discriminating narcoleptic vs. non-narcoleptic patients. These findings are however most probably strongly biased by "circular reasoning" in such a retrospective study design. Increasing the limit to 3 or more SOREMP resulted in a higher specificity and positive predictive value (98%/96% and 100% respectively, however in a relatively low sensitivity (65% and 45% respectively) in discriminating narcoleptic vs. non-narcoleptic patients. A reliable differentiation between NT1 and NT2 with these parameter was however not possible, as expected, due to the similar electrophysiological diagnostic criteria [2].

These findings are perfectly in line with literature: Aldrich et al. reported a sensitivity and specificity of 3 or more SOREMP in MSLT of 48% and 98%, and SOREMP in PSG of 29% and 98% [15]. Andlauer et al. reported a sensitivity and specificity of 51% and 99% for PSG SOREMP in patients with NT1 vs. population based controls [10].

In a study by Drakatos et al. SOREMP occurred in NT1 patients in 63% of all MSLT naps, in NT2 in 60%, in IH in only 1% and in ISS patients in 7% [9]. Furthermore, a relatively homogeneous temporal distribution of SOREMP occurrence during the course of an MSLT day was shown for NT1 and NT2 [9]. In line with these results, we found proportions of narcolepsy, especially NT1 patients with SOREMP occurring in individual MSLT naps relatively evenly distributed throughout the course of the MSLT examination day (78% in MSLT nap 1 decreasing to 65% in MSLT nap 5). However, a statistical comparison of this temporal distribution to occurrence of SOREMP in non-narcoleptic groups was not rational, due to the very small total numbers of detected SOREMP in the non-narcoleptic groups. Therefore, the hypothesis of a narcolepsy specific pattern of temporal distribution of SOREMP in MSLT can neither be confirmed nor rejected, due to a too small non-narcoleptic control group experiencing SOREMP in MSLT.

We found valuable MSLT and PSG criteria distinguishing narcoleptic from non-narcoleptic CDH patients. However, none of the investigated parameter allowed to distinguish NT1 from NT2 and the big overlap of all parameters such as sleep latency between the diagnostic groups in our cohort, supports literature criticism on the official electrophysiological gold standard criteria in diagnosing CDH patients[16]. Our data underline once again the importance of detailed history taking and clinical judgement in the diagnostic workup of CDH patients. Furthermore, a revision of current

Journal Pre-proof

concept of CDH with better clinical, electrophysiological or biological markers would be needed [17,18].

Multiple studies on PSG and MSLT characteristics of patients with EDS have been published so far. However, studies with very large cohorts of up to 2500 subjects[19–21] either describe overall population based results without going into detail of CDH diagnostic groups or are not especially focused on narcolepsy and narcolepsy related disorders. Other studies, comparing CDH patients and other sleepy patient groups, mostly have limited numbers of study population between 20 to 90 patients per diagnostic group[8,9,22], often comparing only 2 to 3 CDH diagnostic groups. Studies on NOH patients are rare[14]. Therefore, the main strength of this study is the relatively large number of included patients with mostly full data sets on PSG and MSLT data, including NOH patients. The major limitations of this study are the retrospective study design, and the lack of interpretation of other available data such as subjective measures of sleepiness (e.g. Epworth Sleepiness Scale), disease onset, treatment status and the lack of follow up data.

Conclusion

In conclusion, NT1 more than NT2 patients have shorter mSL and more frequent SOREMP in MSLT and shorter SL as well as REML during nocturnal PSG. The more SOREMP occur in MSLT and PSG the higher is the probability of discriminating narcoleptic from non-narcoleptic CDH patients, but increasing this limit resulting in greater specificity is at the expense of lower sensitivity. SOREMP occurred evenly distributed throughout a day of 5 MSLT naps in narcolepsy, including the PSG, especially in NT1 patients. Therefore, frequency and temporal distribution of SOREMP in MSLT naps and PSG can help to discriminate but not clearly separate narcoleptic from non-narcoleptic patients. It remains essentially important to carefully phenotype patients clinically as well as electrophysiologically, besides research approaches to find novel biomarkers as well as investigation on pathophysiology of the different CDHs.

Journal Pre-proof

Disclosure statement

This was an industry supported study (financial Support by Jazz Pharmaceuticals). The authors have indicated no financial conflicts of interest.

Acknowledgments

We would like to thank Markus Schmidt, MD, PhD (University Hospital Inselspital, Department of Neurology, Bern) for critically reviewing the manuscript, Dr. Corrado Bernasconi (University Hospital Inselspital, Department of Neurology, Bern) for advice and assistance with statistical workup, and Prof. Limoni (Net-Megs, USI Lugano) for his advice and statistical assistance.

Journal Pre-proof

Journal Pre-proof

References

[1] Ohayon MM, Dauvilliers Y, Reynolds CF. Operational Definitions and Algorithms for Excessive Sleepiness in the General Population. Arch Gen Psychiatry 2012;69:71. https://doi.org/10.1001/archgenpsychiatry.2011.1240.

[2] American Association of Sleep Medicine. International Classification of Sleep Disorders (ICSD3) - 3rd Edition (2014). 3rd ed. Darien, Illinois: 2014.

[3] Hossain JL, Shapiro CM. The Prevalence, Cost Implications, and Management of Sleep Disorders: An Overview. Sleep Breath 2002;6:85–102. https://doi.org/10.1007/s11325-002-0085-1.

[4] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.

[5] Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT 2005;28:123–44.

[6] Mignot E, Lin L, Finn L, Lopes C, Pluff K, Sundstrom ML, et al. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. Brain 2006;129:1609–23. https://doi.org/10.1093/brain/awl079.

[7] Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. Sleep Med 2004;5:339–43. https://doi.org/10.1016/j.sleep.2004.01.021.

[8] Marti I, Valko PO, Khatami R, Bassetti CL, Baumann CR. Multiple sleep latency measures in narcolepsy and behaviourally induced insufficient sleep syndrome. Sleep Med 2009;10:1146–50. https://doi.org/10.1016/j.sleep.2009.03.008.

[9] Drakatos P, Suri A, Higgins SE, Ebrahim IO, Muza RT, Kosky CA, et al. Sleep stage sequence analysis of sleep onset REM periods in the hypersomnias. J Neurol Neurosurg Psychiatry 2013;84:223–7. https://doi.org/10.1136/jnnp-2012-303578.

[10] Andlauer O, Moore H, Jouhier L, Drake C, Peppard PE, Han F, et al. Nocturnal rapid eyemovement sleep latency for identifying patients with narcolepsy/hypocretin deficiency. JAMA Neurol 2013;70:891–902. https://doi.org/10.1001/jamaneurol.2013.1589.

[11] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208. https://doi.org/10.1016/J.JBI.2019.103208.

[12] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81. https://doi.org/10.1016/J.JBI.2008.08.010.

[13] Dauvilliers Y, Lopez R, Ohayon M, Bayard S. Hypersomnia and depressive symptoms: methodological and clinical aspects. BMC Med 2013;11:78. https://doi.org/10.1186/1741-7015-11-78.

[14] Kofmel NC, Schmitt WJ, Hess CW, Gugger M, Mathis J. Sleepiness and Performance Is Disproportionate in Patients with Non-Organic Hypersomnia in Comparison to Patients with Narcolepsy and Mild to Moderate Obstructive Sleep Apnoea. Neuropsychobiology 2014;70:189–94. https://doi.org/10.1159/000365486.

[15] Aldrich M, Chervin R, Malow B. Value of the Multiple Sleep Latency Test (MSLT) for the Diagnosis of Narcolepsy. Sleep 1997;20. https://doi.org/10.1093/sleep/20.8.620.

[16] Mayer G, Lammers GJ. The MSLT: More objections than benefits as a diagnostic gold standard? Sleep 2014;37:1027–8. https://doi.org/10.5665/sleep.3748.

[17] Fronczek R, Arnulf I, Baumann CR, Maski K, Pizza F, Trotti LM. To Split or to Lump? Classifying the Central Disorders of Hypersomnolence. Sleep 2020. https://doi.org/10.1093/sleep/zsaa044.

[18] Lammers GJ, Bassetti CLA, Dolenc-Groselj L, Jennum PJ, Kallweit U, Khatami R, et al. Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts. Sleep Med Rev 2020;52:101306. https://doi.org/10.1016/j.smrv.2020.101306.

[19] Chervin RD, Aldrich MS. Sleep onset REM periods during multiple sleep latency tests in patients evaluated for sleep apnea. Am J Respir Crit Care Med 2000;161:426–31. https://doi.org/10.1164/ajrccm.161.2.9905071.

[20] Cairns A, Trotti LM, Bogan R. Demographic and nap-related variance of the MSLT: results from 2,498 suspected hypersomnia patients: Clinical MSLT variance. Sleep Med 2019;55:115–23. https://doi.org/10.1016/j.sleep.2018.12.013.

[21] Goldbart A, Peppard P, Finn L, Ruoff CM, Barnet J, Young T, et al. Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort. Sleep 2014;37:1043–51. https://doi.org/10.5665/sleep.3758.

[22] Murer T, Imbach LL, Hackius M, Taddei RN, Werth E, Poryazova R, et al. Optimizing MSLT Specificity in Narcolepsy With Cataplexy. Sleep 2017;40. https://doi.org/10.1093/sleep/zsx173.

Journal Pre-proof

Journal Pre-proof

Table 1 Demographics, clinical patient description

	NT1	NT2	IH	NOH	ISS
n	97	31	48	116	78
Male/female	61/36	22/9	15/33	43/73	45/33
Median Age in years (IQR)	36 (27)	32 (20)	24 (8.5)	38 (22)	28 (22)
HLA DQB1*06:02 positive/available	66/67	15/28	3/24	n.d.	n.d.
Hypocretin measured	18	7	n.d.	n.d.	n.d.
Median Hypocretin (range) pg/ml	0 (0-35)	293 (293-376)			

Table legend: *NT1* narcolepsy type 1, *NT2* narcolespy type 2, *IH* idiopathic hypersomnia, *NOH* nonorganic hypersomnia, *ISS* insufficient sleep syndrome, *IQR* interquartile range.

Journal Pre-proof

Journal Pre-proof

Table 2 Proportions of patients with SOREMP in MSLT and PSG

	NT1	NT2	IH	NOH	ISS
n patients with MSLT	84	31	48	97	53
n patients with MSLT SOREMP any MSLT nap*	77 (92, 84-96)	29 (94, 78-98)	6 (13, 6-25)	13 (13, 8-22)	8 (15, 8-28)
MSLT nap 1**	78 (68-86)	65 (47-79)	9 (3-21)	9 (4-16)	4 (1-15)
MSLT nap 2	66 (55-76)	52 (35-68)	2 (0-14)	5 (2-12)	2 (0-13)
MSLT nap 3	66 (55-75)	43 (27-61)	0	3 (1-9)	4 (1-14)
MSLT nap 4	63 (52-72)	61 (43-77)	4 (1-15)	3 (1-9)	8 (3-19)
MSLT nap 5	65 (55-75)	17 (7-34)	0	4 (2-11)	4 (1-15)
n (%) patients with number of MSLT SOREMP					
0 SOREMP	7 (8)	2 (7)	42 (88)	84 (87)	45 (85)
1 SOREMP	6 (6)	3 (10)	5 (10)	6 (6)	6 (11)
2 SOREMP	9 (11)	14 (45)	1 (2)	5 (5)	1 (2)
3 SOREMP	18 (21)	7 (23)	0 (0)	2 (2)	1 (2)
4 SOREMP	25 (30)	5 (16)	0 (0)	0 (0)	0 (0)
5 SOREMP	20 (24)	0 (0)	0 (0)	0 (0)	0 (0)
n patients PSG	93	29	45	110	74
n patients with PSG SOREMP*	49 (53, 43-63)	6 (21, 10-39)	0 (0)	0 (0)	0 (0)

Table legend: *MSLT* Multiple Sleep Latency Test*, PSG* Polysomnography*, SOREMP* Sleep Onset REM Period*, NT1* narcolepsy type 1, *NT2* narcolepsy type 2, *IH* idiopathic hypersomnia, *NOH* nonorganic hypersomnia, *ISS* insufficient sleep syndrome, *Data are n, % (95% CI), **Data are proportions of patients in % (95% CI). *MSLT* Multiple Sleep Latency Test

Journal Pre-proof

Figure 1 Comparison of Sleep and REM Latency in MSLT and PSG between groups

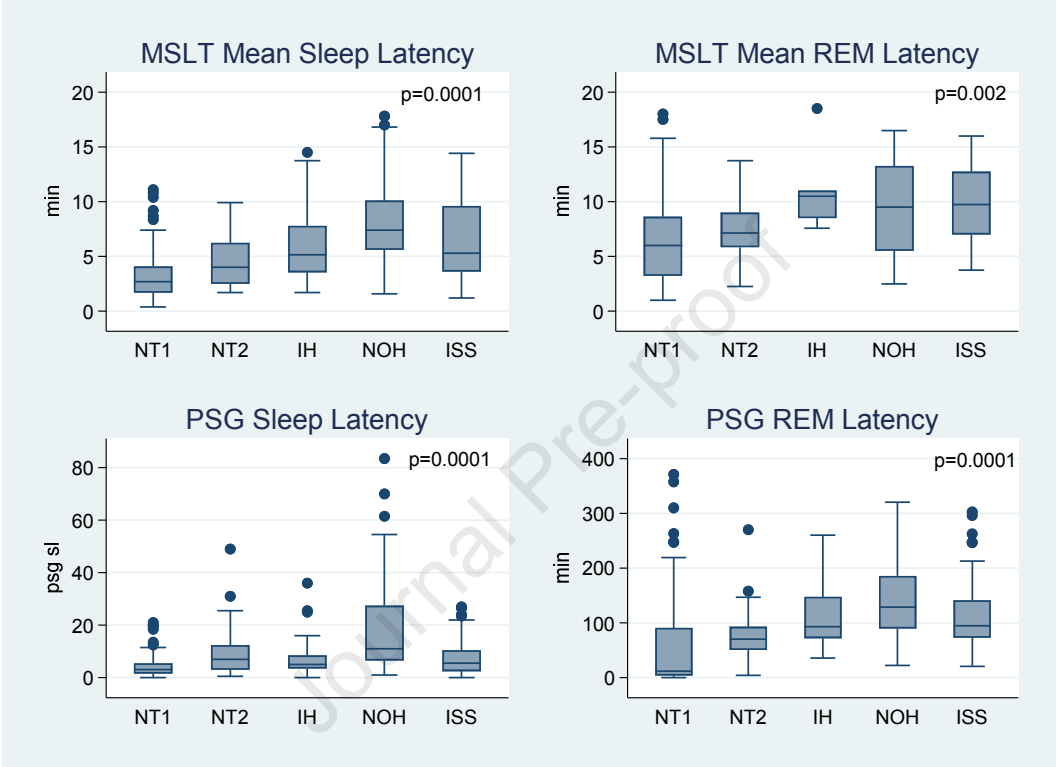

Figure legend: *MSLT* Multiple Sleep Latency Test*, PSG* Polysomnography*, REM* rapid eye movement, *NT1* narcolepsy type 1, *NT2* narcolepsy type 2, *IH* idiopathic hypersomnia, *NOH* nonorganic hypersomnia, *ISS* insufficient sleep syndrome. Kruskal-Wallis equality-of pupulations rank test. *boxes* medians and interquartile ranges.

Journal Pre-proof

Table 3: Sensitivity, specificity and positive predictive value of SOREMP in MSLT and PSG for narcoleptic vs. non-narcoleptic patients.

Cutoff parameter	Narcoleptic patients (n)	Non-narcoleptic patients (n/N)	*p* value*	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)
≥ 2 SOREMP in MSLT and/or PSG°	99/110	10/186	<0.0001	90% (83-95)	95% (90-97)	91% (84-95)
≥ 3 SOREMP in MSLT and SOREMP in PSG	42/110	0/186	<0.0001	38% (29-48)	100% (98-100)	100%
≥ 3 SOREMP in MSLT	75/115	3/198	<0.0001	65% (56-74)	98% (96-100)	96% (89-98)
SOREMP in PSG	55/122	0/229	<0.0001	45% (36-54)	100% (98-100)	100%

Table legend: *SOREMP* Sleep Onset REM Period, *MSLT* Multiple Sleep Latency Test, *PSG* Polysomnography, PPV *positive predictive value,* *χ^2 test, °according to ICSD3 diagnostic criteria[2]

Journal Pre-proof

Journal Pre-proof

Highlights

Manuscript: Multiple Sleep Latency Test and Polysomnography in Patients with Central Disorders of Hypersomnolence

- SOREMP, especially in PSG occur far more frequently in narcoleptic patients
- However, also other sleepy CDH patients may have up to 3 SOREMP in MSLT/PSG
- In NT patients SOREMP occur evenly distributed throughout a day of 5 MSLT naps
- SOREMP help but not discriminate narcoleptic from non-narcoleptic sleepy patients
- History taking and clinical patient evaluation is essential in diagnosing CDH patients

Journal Pre-proof

Journal Pre-proof

CRediT Author Statement

Multiple Sleep Latency Test and Polysomnography in Patients with Central Disorders of Hypersomnolence

Anelia Dietmann: Term, Conceptualization, Resources, Investigation, Visualization, Formal analysis, Writing – Original Draft, Project administration

Camilla Gallino: Formal analysis, Visualization, Writing – Original Draft, Review & Editing

Elena Wenz: Formal analysis, Visualization, Writing – Review & Editing

Johannes Mathis: Methodology, Writing – Review & Editing

Claudio L. A. Bassetti: Term, Conceptualization, Writing – Review & Editing, Funding acquisition

Journal Pre-proof